REMARKS

Claims 1-38 are pending in the present application. Claim 1 recites a method of assessing a patient's risk of having a fetus with a fetal abnormality by using the patient's BPD/OFD ratio and at least one other secondary marker during the first trimester of pregnancy.

Claims 1-38 stand rejected for being allegedly rendered obvious by U.S. Patent No. 6,573,103 to Wald ("Wald") in view of Stempfle *et al*, "Skeletal abnormalities in fetues with Down's syndrome: a radiographic post-mortem study," Ped. Radiology, 29:682-688 (1999) ("Stempfle"). Applicant traverse this rejection at least because there is no reasonable expectation of success in using the BPD/OFD measurement, as described by Stempfle, as a marker for fetal abnormalities, in accordance with the methods of Wald.

Specifically, as shown in the articles attached as Exhibits A-C, previous studies that analyzed the BPD/OFD ratio (also referred to as the "cephalic index") determined that it was not an effective marker for Down's Syndrome. For example, Lockwood *et al.* (Exhibit A) examined a group of ultrasound markers and concluded that there were no statistically significant differences in the BPD/OFD ratio ("cephalic index")[1] between control fetuses and Down's Syndrome fetuses between 15 and 23 weeks gestation (see Lockwood et al, Am J. Obstet Gynecol, 157:803-808, 805, 807 (1987)). As noted by Lockwood *et al*, these results were consistent with another study evaluating BPD/OFD ratio ("Perry et al, however, were not able to differentiate normal from Down syndrome fetuses on the basis of an increased cephalic index during second-trimester sonography. Our data confirm their observation, with no difference in cephalic index noted between case and control populations." (page 807)).

Similar results were obtained by Borrell *et al.* (Exhibit B), who evaluated fetuses at 13-18 weeks gestation and found that the comparison between control fetuses and Down syndrome fetuses did not show a significant difference in cephalic index[2] (see Borrell et al., "Brachycephaly is ineffective for detection of Down syndrome in early midtrimester fetuses," Early Human Dev. 47:57-61, 60 (1996)).

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[1] Lockwood *et al.* calculate cephalic index by dividing the biparietal diameter by the occipitofrontal diameter measured at the same level (see page 804).

[2] The cephalic index in Borrell et al. was calculated as the ratio of BPD/OFD (see page 58).

Similar results were also obtained by Rosati and Guarglia (Exhibit C), who evaluated fetuses between 9 and 16 weeks gestation and concluded that early in pregnancy the cephalic index[3] cannot be considered a useful tool in the detection of fetuses at risk for Down syndrome (see Rosati and Guariglia, "Early Transvaginal Measurement of Cephalic Index for the Detection of Down Syndrome Fetuses," Fetal Diag.Therapy, 14:38-40, 38 (1999)).

Therefore, based on the knowledge available prior to the filing date of the present application, one skilled in the art would not have had a reasonable expectation that the BPD/OFD ratio would be an effective marker for Down's Syndrome.

Further, Applicants submit that Stempfle does not provide this reasonable expectation of success. Stempfle's conclusions are based on radiographic studies of post mortem Down Syndrome fetuses, not on ultrasound examinations. Furthermore, Stempfle certainly does not provide a reasonable expectation that the BPD/OFD ratio would be a successful marker of Down's Syndrome during the first trimester of pregnancy, as required by the present claims. All of the fetuses studied by Stempfle were during 14-40 weeks gestation (i.e. the second trimester of pregnancy to term) and therefore no results were provided for the first trimester of pregnancy. The second trimester to term results of Stempfle cannot necessarily be extended to the first trimester of pregnancy, in view of the findings of Rosati and Guariglia, who found that the cephalic index is not a useful tool early in pregnancy, and because not all ultrasound markers are necessarily effective at all stages of pregnancy. In other words, it cannot be assumed that results from one stage of pregnancy would necessarily be obtained at another stage of pregnancy. For example, some ultrasound markers are effective in the first but not the second trimester of pregnancy, and other ultrasound markers are effective in the second but not the first trimester of pregnancy.

Specifically, measurements of femur and humerus length are thought to be effective in the second trimester of pregnancy but not the first trimester (see Rodis *et al.*, "Comparison of humerus length with femur length in fetuses with Down syndrome," Am. J. of Obst. And Gyn., 165:1051-1056 (1991) compared to Longo *et al.*, "Femur and humerus length in trisomy 21 fetuses at 11-14 weeks of gestation," Ultrasound Obstet. Gynecol., 23: 143-147 (2004) (Exhibit D and E, respectively). Longo states that during

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[3] The cephalic index in Rosati and Guariglia was also calculated as the ratio BPD/OFD.

the first trimester of pregnancy, the femur and humerus lengths in trisomy 21 fetuses are significantly reduced but the degree of deviation from normal is too small for these measurements to be useful in screening from trisomy 21. (see conclusion, page 143). Rodis *et al.*, however, concluded that humerus length measurements taken during the second trimester of pregnancy could be used to determine fetuses at risk for Down syndrome (see 1055 and 1051 (abstract)).

Nuchal translucency, on the other hand, is thought to be effective in the first trimester of pregnancy but not the second trimester (see Nicholaides, "Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities," Am. J. of Obst. and Gync, 191: 45-67 (2004) (Exhibit F). Nicholaides states that the optimal gestational age for the measurement of fetal NT is during late in the first trimester of pregnancy and the incidence of abnormal accumulation of nuchal translucency is lower during the early second trimester than during the first trimester (see bottom of page 47 to top of page 48).

Therefore, the above-described articles illustrate that ultrasound markers useful during one stage of pregnancy are not necessarily useful at another stage of pregnancy. As such, just because Stempfle provides results of BPD/OFD ratios during the second trimester to term of pregnancy, does not mean that one skilled in the art would expect that those results would be obtained during the first trimester of pregnancy, such that the BPD/OFD ratio would be considered an effective marker during the first trimester of pregnancy. For at least these reasons, Applicants submit that Stempfle does not provide a reasonable expectation that the BPD/OFD ratio would be a successful marker for a fetal abnormality during the first trimester of pregnancy and should therefore be used as an ultrasound marker in the methods of Wald. Accordingly, Applicants submit that claims 1-38 are not rendered obvious by the combination of Wald and Stempfle and Applicants request withdrawal of this rejection.

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,

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